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Human Chitotriosidase in Cardiac Sarcoidosis

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COLUMN ARTICLE

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ABBREVIATIONS

ACE: Angiotensin Converting Enzyme; IL2r: Interleukin 2 Receptor; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; HRCT: High Resolution Computed Tomography of the Chest

Cardiac sarcoidosis occurs in about 2 - 10% of sarcoidosis patients although prevalence of this disease varies significantly depending on the population studied and methodology used for detection [1-4]. The manifestations of cardiac sarcoidosis may include conduction abnormalities, heart failure, ventricular and atrial arrhythmias. In Japan, where cardiac sarcoidosis is more common than in western countries, 50 - 70% of these patients died of cardiac events. In the majority of patients with cardiac sarcoidosis, the disease is limited to the heart or it is associated with a minimal extra-cardiac involvement [5]. Early and accurate diagnosis of cardiac involvement is necessary in patients with sarcoidosis to avoid sudden cardiac death and sever cardiovascular events. The diagnostic algorithm is very complex as histological examination of myocardial tissue is hardly practicable [1-6]. The endomyocardial biopsy is falling out of favour due to patchy myocardial involvement, considerable procedure-related risks and advancement in additional imaging modalities [6]. Therefore, diagnosis of cardiac sarcoidosis usually depends on identifying sarcoid granulomas in other tissues with evidence of disease. An indirect diagnosis is based on histological evidence of extracardiac sarcoidosis in a patient with unexplained reduced left ventricular ejection fraction (< 40%), cardiac disease responsive to steroids or immunosuppressant, evidence of granulomatous sarcoidosis alterations on cardiac positron emission tomography (PET) or cardiovascular magnetic resonance or gallium uptake study [6,7]. 18F-FDG PET in particular seems to be very useful in evaluating active cardiac sarcoid lesions and its specificity as diagnostic tool is very high [8]. No serological biomarker with adequate sensitivity and sensibility has been identified to improve the diagnosis of cardiac sarcoidosis and in particularly in patients with isolated cardiac involvement and no possibility to perform an extra-cardiac biopsy there is a need of a specific serological indicator [9]. Several biomarkers, such as cytokines, chemokines and macrophage- or lymphocyte derived mediators including angiotensin converting enzyme (ACE) and interleukin 2 receptor (IL2r) have

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been studied in systemic sarcoidosis (including sIL-2R, serum amyloid A, CRP, and angiotensin-converting enzyme) but few data is available about their expression in cardiac sarcoidosis, as well as in neurosarcoidosis, both manifestations associated with significant morbidity and mortality [10-13]. However, no data is available about neopterin, chitinases and sIL2R in cardiac involvement while few papers report ACE and lysozyme sensitivity in these patients. ACE is reported increased in no more than 37% of patients with cardiac sarcoidosis while lysozyme in about 60% of patients [14]. Baba., *et al*. in 2012 demonstrated that high sensitive cardiac troponin T was a better biomarker than ACE and lysozyme being increased in 8/12 patients with cardiac sarcoidosis (87.5%) [15].

In Christchurch hospital, angiotensin-converting enzyme (ACE) and cardiac troponin concentrations were detected in 18 patients to help the diagnosis but unfortunately, they were increased only in 25% and 30% of patients with cardiac sarcoidosis, respectively. All these studies underlined the necessity of a specific biomarker with an adequate sensitivity to help the diagnosis of cardiac sarcoidosis and to predict disease severity [14-21].

At the University Hospital of Florence, we retrospectively analyzed serum biomarkers of sarcoidosis in 6 patients with cardiac involvement diagnosed in the last 36 months. Four patients were male, mean age was 44,2 ± 7,9 (M ± DS), they were no smoker only one was ex-smoker. Three of these young patients had an asymptomatic cardiac localization discovered after a total body PET demonstrating in all cases a pulmonary, lymph node and cardiac sarcoidosis and in a patient also salivary glands localizations. Diagnosis of cardiac involvement was furtherly confirmed by cardiac nuclear magnetic resonance and mediastinal lymph node biopsy. The fourth patient presented an acute ventricular tachycardia induced under strain during a basket match. Cardiac nuclear magnetic resonance confirmed the presence of catting granulomas as well as PET that allowed also the discovery of hepatic and spleen involvements. Hepatic granulomas histologically confirmed allowed to perform the diagnosis of cardiac sarcoidosis. The fifth patient was a female and she referred severe dyspnea and recurrent episodes of arrhythmias. The patient presented normal lung function parameters with a mild reduction of DLCO percentage (65%). High resolution computed tomography of the chest revealed the presence of bilateral micro nodules, ground glass opacities and consolidation in the upper lung lobes. Supraventricular tachycardia was registered through 24h Holter monitor and magnetic resonance imaging (MRI) revealed diffuse myocardial thickening and intra-myocardial focal zones with high signal intensity. The last patient with undiagnosed sarcoidosis presented an acute onset of the disease with chest pain, breathing and severe ventricular tachycardia requiring endocardial ablation and defibrillator. The diagnosis was performed by cardiac MRI and confirmed by broncho alveolar lavage (increased lymphocyte percentage greater than 40% were associated with CD4/CD8 ratio 4.8) and bronchial biopsy demonstrating sarcoidosis granulomas. PET, echo abdomen and high resolution computed tomography (HRCT) of the chest confirmed pulmonary sarcoidosis and minimal spleen involvement.

In all six patients, serological analysis of ACE, C-reactive protein and chitotriosidase were performed at the onset (before starting steroid therapy). None of them presented increased ACE concentrations that resulted 41.11 ± 25.35 U/l (normal values < 65U/l), they have normal CRP levels (< 8mg/l), only serum chitotriosidase was highly increased in all cases with mean concentrations 169.54 ± 98.76 nmol/h/ml (normal values 45 nmol/h/ml). Interestingly the highest values of chitinase 1 (greater than 200) were observed in the last 3 patients who also presented the highest PET positivity and greater cardiac MRI involvement. Although in a limited population, chitotriosidase for the first time was reported increased in patients affected by cardiac sarcoidosis; this chitinase needs to be further studied in larger population as it may help to distinguish sarcoidosis from systemic diseases associated with cardiac involvement [22,23]. In fact, several research studies suggest that very high enzyme levels (10 folds greater than controls as in our patients) are present only in sarcoidosis and not in other inflammatory systemic disorder including granulomatosis [22-26].

Further studies in a larger population cohort are required to evaluate human chitotriosidase levels in active

cardiac disease [24-26] to verify our observation and to clarify its role in the pathogenesis of the disease.

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